



Office de la propriété
intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An Agency of
Industry Canada

PCT/CA

33 / 00066

REC'D 10 FEB 2003

WIPO

PCT

Rec'd PCT/PTO

19 JUL 2004

*Bureau canadien
des brevets
Certification*

*Canadian Patent
Office
Certification*

La présente atteste que les documents
ci-joints, dont la liste figure ci-dessous,
sont des copies authentiques des docu-
ments déposés au Bureau des brevets.

This is to certify that the documents
attached hereto and identified below are
true copies of the documents on file in
the Patent Office.

Specification as originally filed, with Application for Patent Serial No: 2,368,656, on
January 21, 2002, by **VASOGEN IRELAND LIMITED**, assignee of Anthony E. Bolton
and Arkady Mandel, for "Receptor-Ligand Pairing for Anti-Inflammatory Response".

**PRIORITY
DOCUMENT**

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

S. Gregoire
Agent certificateur/Certifying Officer

December 13, 2002

Date

Canada

(C/PO 68)
04-09-02

OPIC CIPO

BEST AVAILABLE COPY

ABSTRACT OF THE DISCLOSURE

A composition of matter capable of producing an anti-inflammatory response *in vivo* in a mammal comprises bodies having a three-dimensional core structure of conformation and size corresponding to mammalian apoptotic cells and/or bodies and expressing or expressible on the surface thereof a plurality of the same or different ligands which will react, optionally in the presence of adapter molecules, with at least one specific receptor wherein the binding of said ligand(s) with said receptors produces an anti-inflammatory response *in vivo* in said mammal, with the proviso that when said ligands are of the same type, said ligands are not PS.

RECEPTOR-LIGAND PAIRING FOR ANTI-INFLAMMATORY RESPONSE

Field of the invention

This invention relates to medical and pharmaceutical compositions and medical treatments. More specifically, the invention relates to compositions which, on administration to mammalian patients, exert beneficial effects on a patient's immune system.

Background of the invention

During the normal physiological processes occurring during the life of a mammalian body, cells that become senescent die by a process of programmed cell death also called apoptosis. These dying cells are removed from the body, generally by some type of antigen presenting cell, often to be replaced by cells newly produced by cell division. This is part of the normal cell turnover in the mammalian body. Unlike cells that die by necrotic cell death as a result of a pathological process, such as trauma or infection, cells dying by apoptosis do not elicit an inflammatory response. Indeed, it has recently been demonstrated that cells undergoing apoptosis can exert an actively anti-inflammatory response on the immune system in that they can induce a down-regulation of certain inflammatory cytokines and/or up-regulation of certain anti-inflammatory cytokines (Fadok, Valerie A. et. al., Nature, Vol. 405, 4 May 2000, p85; Scott, Rona S. et.al., Nature, Vol. 411, 10 May 2001, p207).

In the process of apoptosis, the dying cells undergo a change in morphology and in the expression of various ligands present on the outer surface of the cell membrane. These changes in cell surface ligand expression are thought to signal to those cells of the body that remove apoptotic cells. A number of specific ligands expressed on apoptotic cells have been observed to induce an anti-inflammatory response as a consequence of interaction with receptors, in antigen presenting cells, for example by inducing the down-regulation of certain inflammatory cytokines and/or the up-regulation of certain anti-inflammatory cytokines by antigen presenting cells. There are a number of cell surface ligands which are present either

- 5 uniquely or at increased levels on apoptotic cells compared to normal cells: These include phosphatidylserine (PS), a phospholipid normally restricted to the inside of the cell membrane but which becomes transferred to the outside of the membrane during apoptosis, and interacts with PS receptors on antigen presenting cells.
- 0 The result of the process of interaction of ligands and receptors in the process of apoptotic death of cells in the mammalian body is a change in the cytokine production profile of various cells in the mammalian immune system, especially the antigen presenting cells involved in the uptake of the products of apoptosis.

Summary of the Invention

The present invention is based on the discovery that the interaction of one or more receptors on antigen presenting cells with a specific ligand or ligands expressed or up-regulated during the apoptotic cell death process, alters the cytokine production profile of the antigen presenting cells and other cells capable of cytokine production *in vivo*. Depending on the particular receptor-ligand interaction, this leads to either an increase in anti-inflammatory cytokines or a decrease in pro-inflammatory cytokines, or both. The present invention proceeds from this discovery, and comprises the therapeutic application of compositions of matter containing surface ligands, other than or in addition to PS, that are those expressed by cells undergoing cell death by apoptosis, or are recognized by one or more of the receptors. Such ligands will interact with receptors on antigen presenting cells to promote an anti-inflammatory response. The invention comprises the novel compositions of matter, their processes of preparation, their therapeutically useful forms, combinations and compositions, and their therapeutic uses. As a result of the administration of these compositions of matter, an inflammatory - autoimmune, cardiovascular and/or neurodegenerative disorder in a mammalian patient is treated or inhibited. The composition presents or is induced to present *in vivo* an appropriate ligand or combination of ligands which act in a manner analogous to

5 those ligands presented on the surface of cells undergoing apoptosis. It is postulated that, upon interaction with a specific receptor or receptors on cells of the recipient mammalian patient (other than or in addition to PS receptors), the cytokine profile of the antigen presenting cells of the mammalian patient is altered by upregulation of one or more anti-inflammatory cytokines and/or down-regulation of one or more inflammatory cytokines. This induces, among other effects, a shift in the balance of the T-cells of the recipient patient's body such that there is a relative increase in regulatory T-cells such as Th-2, Th-3, Tr-1 and/or other regulatory cell populations, and/or a relative decrease in pro-inflammatory T-cells such as Th-1 cells. In this way, the immune system of the recipient mammalian patient is modulated, altering the cytokine profile towards a less inflammatory or an anti-inflammatory profile, in a manner towards alleviation or inhibition of the specific disorder under treatment.

Thus according to one aspect of the present invention, there is provided

Another aspect of the invention provides a process of alleviating or inhibiting the symptoms of inflammation in a mammalian patient (preferably a human patient and more preferably an adult human patient), which comprises administering to the patient an effective amount of a composition of matter comprising bodies having a three-dimensional core structure of conformation and size corresponding to mammalian apoptotic bodies and carrying on the surface thereof a plurality of the same or different ligands which will react, optional in the presence of adapter molecules, with at least one specific receptor wherein the binding of said ligand(s) with said receptors produces an anti-inflammatory response *in vivo* in said mammal, with the proviso that when said ligands are the same, said ligands are not PS.

THE PREFERRED EMBODIMENTS

- 5 A composition of matter comprising bodies having a three-dimensional core structure of conformation and size corresponding to mammalian apoptotic bodies, as the term is used herein, refers to a biocompatible composition of matter having a three-dimensional body portion of shapes and dimensions ranging from those resembling mammalian cells to shapes and dimensions approximating to apoptotic bodies produced by apoptosis of mammalian cells (typically but not exclusively spheroidal, cylindrical, ellipsoidal including oblate and prolate spheroidal, serpentine, reniform, etc., and from about 20 nanometers to about 500 microns in diametric dimension). They have one or more ligands of predetermined characteristics presented on the exterior surface in a manner for interaction with appropriate receptor(s), preferably other than exclusively the PS receptor, on professional or other antigen-presenting cells in vivo.

Examples of three-dimensional body portions include liposomes, solid beads, hollow beads, filled beads, natural vesicles such as cell ghosts, exosomes, which are microvesicles exfoliated from cultured cells, and may also be produced in vivo, e.g. during maturation of reticulocytes (see Trams et.al, *Biochimica et Physica Acta*, 645 (1981) 63 - 70; and also Johnstone, *Biochem. Cell. Biol.*, 70 (1982) 179 -190); prostasomes, which are vesicular extracellular organelles found in seminal plasma (see Rooney et.al, *J. Exp. Med.*, 177, May 1993, 1409 - 1420); apoptotic cells and apoptotic bodies presenting ligands other than or additional to PS; spontaneous or induced shed membrane vesicles, i.e. membrane vesicles shed from cells as a result of inducement using detergents such as lysophosphatidylcholine, or spontaneously (see Ferber et.al., *Biochimica et Biophysica Acta*, 595 (1980) 244 - 256; also Emerson et.al., *The Journal of Immunology*, 127(2) , August 1981, 482 - 486); procoagulant bound to plasma membrane vesicles, i.e. thromboplastin-like activity associated with membrane vesicles, found for example in bronchoalveolar lavage fluid and derived from alveolar macrophages (see Lyberg et.al, *Eur. Respir. J.*, 3 (1990), 61 - 67); inside out red blood cell ghosts (see Schroit et.al, *Biol. Cell* 51 (1984) 227 - 238); erythrocytes with lost phospholipid asymmetry, i.e. erythrocytes with randomized, symmetric transbilayer distribution of phospholipids; these can be produced, for example, by elevating intracellular

5 Ca++ levels (see Pradham et.al. Molecular Membrane Biology 11 (1994) 181 -188);
activated platelets, platelets with pro-coagulant activity, (see Bevers et.al., Biochimica et
Biophysica Acta, 736: (1983) 57 - 66); platelet derived microparticles, which are
membranous vesicles or microparticles shed from platelet membranes following platelet
activation (see Gilbert et.al., The Journal of Biological Chemistry, 266 No.26, Sept. 16,
10 1991, 17261 - 17268). Preferably the three-dimensional bodies are not apoptotic cells or
apoptotic bodies.

Natural vesicles may have the required ligand naturally present on their surfaces, or may
require chemical synthetic modification to introduce the required ligand onto their surfaces.
15 Synthetic body portions such as liposomes and beads can be prepared synthetically to have
the required ligand on their surfaces.

Preferred compositions of matter are liposomes, e.g. liposomes of phospholipids constituting
the membranes (phosphatidyl choline, etc., but not exclusively or predominantly phosphatidyl
20 serine), carrying the required ligand on the surface thereof. They may be prepared by
chemical modification of a pre-formed liposome.

In the process of using the compositions of the invention to alleviate or inhibit inflammation
in a mammalian body, the compositions are introduced into the body by suitable means, and
then it is believed that the bodies are recognized by antigen-presenting cells and interact
therewith through the reaction of the ligand(s) on the body surfaces with specific receptor(s)
for the ligands on the antigen-presenting cells, followed in most cases by engulfment and
digestion of the bodies by the antigen-presenting cells, in a manner resembling the process of
apoptosis. At some stage in the process consequent upon the ligand-receptor interaction, the
cytokine profile of the involved cells, most probably the antigen-presenting cells, changes in
10 a direction favoring anti-inflammation. The present invention is not dependent upon any
particular theory or mode of action, only on the fact that an anti-inflammatory response is
obtained at some stage in the *in vivo* process following the appropriate administration of the

5 bodies to the patient.

In some instances and in connection with some ligand- receptor pairings, it is believed that the apoptotic process involves a preliminary step of "tethering" of the apoptotic cell or body to the antigen presenting cell (commonly a macrophage, a dendritic cell or other non-professional antigen-presenting cell such as an endothelial cell or a B-cell) using a different ligand for initial attachment, followed by reaction of the specific receptor with the corresponding ligand to those expressed on apoptotic bodies and/or cells, which may be different from the tethering ligand. The present invention extends to such situations, and covers cases where the bodies carry tethering ligands for interaction with professional antigen presenting cells and non-professional antigen presenting cells, resulting in an anti-inflammatory response.

Examples of PS receptors are disclosed in Fadok, V., et. al., International patent application publication WO-01/66785, published 13 September, 2001.

In some cases also, it is necessary or desirable to have adapter or activator molecules present in the system, to enhance the activity of the receptor on the antigen presenting cells towards its specific ligand. The present invention extends to cover cases where there is an endogenous population of active receptors continuously present *in vivo*, and where such population is induced *in vivo* prior to or simultaneously with the introduction of ligand as a component of the bodies of the present invention, such as would occur by addition of an activator molecule which stimulates the expression of receptor. This can be important in the case of transitory receptors. Examples of proteins which are candidates as adaptor proteins include glyceraldehyde-3-phosphatedehydrogenase-GraP-DH; Paxillin; CrkII; CAS; ADAP; and protein ELMO.

More than one receptor may be involved in interaction with ligands on the bodies according to the present invention, to result in an anti-inflammatory response. The present invention

5 extends to cover this situation, including situations where one of the plurality of involved receptors is the PS receptor.

The following are examples of ligands which can be present on the surface of a liposome, bead or natural vesicle to constitute a composition of matter in accordance with the present invention. This list is by no means exhaustive, and the present invention is not limited to compositions carrying these specific ligands:

- Peptides containing the integrin recognition motif RGDS;

- thrombospondin, which interacts with integrin α_3 receptors on macrophages, to alter the cytokine profile of the macrophages in favor of anti-inflammatory upregulation (Fadok, V.A. et. al., *J. Immunol.*, 1992 Dec. 15; 149(12):4029-35; and Fadok, V.A. et. al., *J. Biol. Chem.*, 2001 Jan 12:276(2): 271, 1071-7); and with integrin α_5 receptors on dendritic cells, to alter the cytokine profile of the dendritic cells in favor of anti-inflammatory upregulation (Albert, M.L. et.al., *Nat. Cell Biol.*, 2000 Dec., 2(12):899-905);

- complement and signaling proteins, for example CRKII, DOCK 180, Rac-1, ELMO1 and ELMO2 (ced-12), at least some of which form a molecular complex to activate Rac-1 and initiate a pathway to apoptosis, involving interaction with integrin α_3 receptors on macrophages, and in some cases with scavenger receptors such as SREC/ced1 (Albert, op. cit.); Henson, P.M. et.al., *Curr. Biol.* 2001 Oct. 2;11(19),R795-805);

- protein C3bi, which recognizes complement receptors CR3 and CR4 on macrophages;

- acetylated low density lipids (acetylated LDL) and oxidized low density lipids (ox-LDL), polyguanylic acid, which interact with scavenger SRA receptors on macrophages through a tethering mechanism (Platt, N. et. al., *Immunol Lett.* 1999 Jan.; 65(1-2):15-

5 9);

0 - ox-LDL, which interact with scavenger SRB1 receptors and with Croquemort receptors on macrophages, through a tethering mechanism (Hajjar, D.P et. al., *J. Biol. Chem.* 1997 Sept. 12, 272(37): 22975-8; and Schlegel, R.A. et. al., *Cell Death Differ.*, 2001 June, 8(6): 551-63); and with macrosialin/CD68 receptors on macrophages (Sambrano, G.R. et.al., *Proc. Natl. Acad. Sci. USA*, 1995 Feb. 28, 92(5): 1396-1400), and with LOX-1 receptors on endothelial cells through a tethering mechanism (Oka, K. et. al., *Proc. Natl. Acad. Sci. USA*, 1998 Aug. 4, 95(16): 9535-40);

5 - collagens, thrombospondin, oxidized LDL and long chain fatty acids (LCFAs), which interact with the scavenger receptor CD36 on macrophages and dendritic cells in favor of anti-inflammatory upregulation (Acton, S.L et. al., *J.Biol.Chem.*, 1994, 269: 21003-21009);

) - acetylated low density lipoproteins, which interact with SREC/ced1 scavenger receptors on endothelial cells in favor of anti-inflammatory up-regulation (Henson, P.M. et.al., *Curr. Biol.* 2001 Oct. 2; 11(19):R795-805);

- ICAM-3 and LPS, which interact with scavenger receptor CD14 on macrophages through a tethering mechanism (Gregory, C.D., *Curr.Opin.Immunol.*, 2000 Feb; 12(1) 27-34);

- 2-GP 1, which interacts with scavenger receptor 2-GP 1 on macrophages (Price, B.E. et.al., *J.Immunol.*, 1996 Sept. 1, 157(5): 2201-8);

-Gas-6, which interacts with the Mer tyrosine kinase receptor on macrophages (Nakano, T. et. al., *J. Biol. Chem.* 1997 Nov. 21; 272(47):29411-4; and Scott, R.S. et. al.,

5 *Nature* 2001 May 10, 411(6834): 207-211)

0 In the present invention, the bodies are acting as modifiers of the patient's immune system, in a manner somewhat similar to that of a vaccine. Accordingly, they are used in quantities and by administration methods to provide a sufficient localized concentration of the bodies at the site of introduction to initiate the appropriate immune response. Quantities of ligand-carrying bodies appropriate for immune system modifying substances are generally not directly correlated with body size of the recipient and can, therefore, be clearly distinguished from drug dosages, which are designed to provide therapeutic levels of active substances in the patient's blood stream and tissues. Drug dosages are accordingly likely to be much larger than immune system modifying dosages.

Preferred ligand carrying bodies for use in the invention are liposomes of the appropriate size and biocompatibility.

Methods of preparing liposomes of the appropriate size are known in the art and do not form part of this invention. Reference may be made to various textbooks and literature articles on the subject, for example, the review article "Liposomes as Pharmaceutical Dosage Forms", by Yechezkel Barenholz and Daan J. A. Chrommelin, and literature cited therein, for example New, R. C. "Liposomes: A Practical Approach", IRL Press at Oxford University Press (1990).

The diameter of the ligand-carrying liposomes of the preferred embodiment of this invention is from about 20 nanometers to about 1000 nanometers, more preferably from about 50 nanometers to about 500 nanometers. Such preferred diameters will generally correspond to the diameters of mammalian apoptotic bodies or apoptotic cells.

Various alternatives to liposomes may be used as ligand-carrying bodies in the present invention. These include particles, granules, microspheres or beads of biocompatible materials, natural or synthetic, such as polyethylene glycol, polyvinylpyrrolidone, polystyrene,

5 etc., polysaccharides such as hydroxethyl starch hydroxyethylcellulose, agarose and the like,
as commonly used in the pharmaceutical industry. Some such suitable substances for
derivatization to attach the ligand are commercially available, e.g. from Polysciences, Inc. 400
Valley Road, Warrington, PA 18976, or from Sigma Aldrich Fine Chemicals. The beads
0 may be solid or hollow, or filled with biocompatible material. They are modified as required
so that they carry ligands on their surfaces.

The ligand-carrying bodies may be administered to the patient by any suitable means
which brings them into operative contact with active components of the patient's immune
system.

5 The ligand-carrying bodies may be suspended in a pharmaceutically acceptable carrier,
such as physiological-sterile saline, sterile water, pyrogen-free water, isotonic saline, and
phosphate buffer solutions, as well as other non-toxic compatible substances used in
pharmaceutical formulations. Preferably, the ligand-carrying bodies are constituted into a
0 liquid suspension in a biocompatible liquid such as buffered saline and administered to the
patient in any appropriate route which introduces it to the immune system, such as intra-
arterially, intravenously or most preferably intramuscularly or subcutaneously.

It is contemplated that the ligand-carrying bodies may be freeze-dried or lyophilized
5 so that they may be later resuspended for administration. This invention is also directed to
a kit of part comprising lyophilized or freeze-dried ligand-carrying bodies and a
pharmaceutically acceptable carrier, such as physiological sterile saline, sterile water,
pyrogen-free water, isotonic saline, and phosphate buffer solutions, as well as other non-toxic
compatible substances used in pharmaceutical formulations.

A preferred manner of administering the ligand-carrying bodies to the patient is a
course of injections, administered daily, several times per week, weekly or monthly to the
patient, over a period ranging from a week to several months. The frequency and duration

5 of the course of the administration is likely to vary from patient to patient, and according to the condition being treated, its severity, and whether the treatment is intended as prophylactic, therapeutic or curative. Its design and optimization is well within the skill of the attending physician.

0 The quantities of ligand-carrying bodies to be administered will vary depending on the nature of the mammalian disorder it is intended to treat and on the identity and characteristics of the patient. It is important that the effective amount of ligand-carrying bodies is non-toxic to the patient, and is not so large as to overwhelm the immune system. When using intra-arterial, intravenous, subcutaneous or intramuscular administration of a
5 liquid suspension of ligand-carrying bodies, it is preferred to administer, for each dose, from about 0.1-50 ml of liquid, containing an amount of ligand-carrying bodies generally equivalent to 10% - 1000% of the number of leukocytes normally found in an equivalent volume of whole blood or the number of apoptotic bodies that can be generated from them. Generally, the number of ligand-carrying bodies administered per delivery to a human patient
) is in the range from about 500 to about 2.5×10^9 (<250 ng of bodies, in the case of liposomes, pro-rated for density differences for other embodiments of bodies), more preferably from about 10,000 to about 50,000,000, and most preferably from about 200,000 to about 10,000,000.

Since the ligand-carrying bodies are acting, in the process of the invention, as immune system modifiers, in the nature of a vaccine, the number of such bodies administered to an injection site for each administration is a more meaningful quantitation than the number or weight of ligand-carrying bodies per unit of patient body weight. For the same reason, it is now contemplated that effective amounts or numbers of ligand-carrying bodies for small animal use may not directly translate into effective amounts for larger mammals (i.e. greater than 5 Kg) on a weight ratio basis.

The present invention is indicated for use in prophylaxis and/or treatment of a wide

5 variety of mammalian disorders where T-cell function, inflammation, endothelial dysfunction
and inappropriate cytokine expression are involved. A patient having or suspected of having
such a disorder may be selected for treatment. "Treatment" refers to administration to a
patient for purposes of achieving a reduction of symptoms, such as, but not limited to, a
decrease in the severity or number of symptoms of the particular disease or to limit further
0 progression of symptoms.

With respect to T-cell function (T-cell mediated) disorders, these may be autoimmune
disorders including, but not limited to diabetes, scleroderma, psoriasis and rheumatoid
arthritis.

5 The invention is indicated for use with inflammatory allergic reactions, organ and cell
transplantation reaction disorders, and microbial infections giving rise to inflammatory
reactions. It is also indicated for use in prophylaxis against oxidative stress and/or ischemia
reperfusion injury, ingestion of poisons, exposure to toxic chemicals, radiation damage, and
exposure to airborne and water-borne irritant substances, etc., which cause damaging
inflammation. It is also indicated for inflammatory, allergic and T-cell-mediated disorders of
1 internal organs such as kidney, liver, heart, etc.

With respect to disorders involving inappropriate cytokine expression for which the
present invention is indicated, these include neurodegenerative diseases. Neurodegenerative
diseases, including Down's syndrome, Alzheimer's disease and Parkinson's disease, are
associated with increased levels of certain cytokines, including interleukin-1 (IL-1) (see Griffin
WST et al. (1989); Mogi M. et al. (1996)). It has also been shown that IL-1 inhibits long-
term potentiation in the hippocampus (Murray, C. A. et al. (1998)). Long-term
potentiation in the hippocampus is a form of synaptic plasticity and is generally considered
to be an appropriate model for memory and learning (Bliss, T.V.P. et al. (1993)). Thus,
inappropriate cytokine expression in the brain is currently believed to be involved in the
development and progression of neurodegenerative diseases.

5 Thus, the invention is indicated for the treatment and prophylaxis of a wide variety of
mammalian neurodegenerative and other neurological disorders, including Downs syndrome,
Alzheimer's disease, Parkinson's disease, senile dementia, depression, Huntingdon's disease,
peripheral neuropathies, Guillain Barr syndrome, spinal cord diseases, neuropathic joint
diseases, chronic inflammatory demyelinating disease, neuropathies including
0 mononeuropathy, polyneuropathy, symmetrical distal sensory neuropathy, neuromuscular
junction disorders, myasthenias and amyotrophic lateral sclerosis (ALS). Treatment and
prophylaxis of these neurodegenerative diseases represents a particularly preferred
embodiment of the invention, with treatment of Alzheimers and Parkinson's disease
particularly preferred.

5 Regarding disorders involving endothelial dysfunction, the present invention is
indicated for the treatment and prophylaxis of a wide variety of such mammalian disorders
including, but not limited to, cardiovascular diseases, such as atherosclerosis, peripheral
arterial or arterial occlusive disease, congestive heart failure, cerebrovascular disease (stroke),
myocardial infarction, angina, hypertension, etc., vasospastic disorders such as Raynaud's
disease, cardiac syndrome X, migraine etc., and the damage resulting from ischemia (ischemic
injury or ischemia-reperfusion injury). In summary, it can be substantially any disorder the
pathology of which involves an inappropriately functioning endothelium.

WHAT IS CLAIMED IS:

1. A composition of matter capable of producing an anti-inflammatory response *in vivo* in a mammal, said composition comprising bodies having a three-dimensional core structure of conformation and size corresponding to mammalian apoptotic cells and/or bodies and expressing or expressible on the surface thereof a plurality of the same or different ligands which will react, optional in the presence of adapter molecules, with at least one specific receptor wherein the binding of said ligand(s) with said receptors produces an anti-inflammatory response *in vivo* in said mammal, with the proviso that when said ligands are all of the same type, said ligands are not PS.
 2. A composition of matter according to claim 1 wherein said bodies are capable of being phagocytosed *in vivo* by mammalian antigen presenting cells, resulting in an alteration of the cytokine profile of cells of the mammalian immune system.
-

- 5 3. Composition of matter according to claim 1 comprising a three-dimensional body
portions selected from liposomes, solid beads, hollow beads and filled beads.
 4. Composition of matter according to claim 1 comprising natural vesicles.
 - 0 5. Composition of matter according to claim 4 wherein the natural vesicles are selected
from cell ghosts, exosomes, prostasomes, procoagulant bound to plasma membrane
vesicles, inside out red blood cell ghosts, sickle cell red blood cells erythrocytes with
lost phospholipid asymmetry, activated platelets, platelets with pro-coagulant activity,
and platelet derived microparticles.
 - 5 6. Composition of matter according to claim 3 comprising a three-dimensional body of
a liposome, and at least one surface ligand selected from:
a peptide containing the integrin recognition motif RGDS,
thrombospondin,
acetylated low density lipoprotein (LDL),
polyguanylic acid,
oxidized low density lipids (LDL)
collagens
long chain fatty acids (LCFAs)
ICAM-3,
2-GP 1,
protein CRKII,
protein DOCK 180,
protein Rac-1
protein ELMO-1,
protein ELMO-2,
protein C3bi;
-

Gas-6.

7. A process of alleviating or inhibiting the symptoms of inflammation in a mammalian patient, which comprises administering to the patient an effective amount of a composition of matter comprising bodies having a three-dimensional core structure of conformation and size corresponding to mammalian apoptotic bodies and expressing or expressible on the surface thereof a plurality of the same or different ligands which will react, optional in the presence of adapter molecules, with at least one specific receptor wherein the binding of said ligand(s) with said receptors produces an anti-inflammatory response *in vivo* in said mammal, with the proviso that when said ligands are the same, said ligands are not PS.
 8. The process of claim 7 wherein the patient's symptoms of inflammation are characteristic of a neurodegenerative disease.
 9. The process of claim 8 wherein the disease is Parkinson's disease.
 10. The process of claim 8 wherein the disease is Alzheimer's disease.
 11. The process of claim 7 wherein the patient's symptoms of inflammation are characteristic of a cardiovascular disease.
 12. The process of claim 11 wherein the disease is atherosclerosis.
-

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.